



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2018-N-0791]

Exposure-Response Analysis in Drug Development and Regulatory Decision Making;

Establishment of a Public Docket; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; establishment of a public docket; request for comments.

SUMMARY: The Prescription Drug User Fee Act of 2017 (PDUFA VI), part of the FDA Reauthorization Act of 2017 (FDARA, highlights the goal of advancing model-informed drug development (MIDD). Exposure-response analysis is a MIDD strategy that has been used in drug development and regulatory decision making. The Food and Drug Administration (FDA or Agency) is opening a docket to receive public comments on experience leveraging exposure-response analysis since publishing the guidance for industry (GFI) entitled "Exposure-Response Relationships--Study Design, Data Analysis, and Regulatory Applications," which was announced in the *Federal Register* on May 6, 2003. Specifically, the Agency wants to identify areas of scientific policy that may need further clarity or elaboration, as well as any obstacles that prevent use of exposure-response analyses in drug development and regulatory review.

DATES: To ensure that the Agency considers your input, submit either electronic or written comments by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments as follows. Electronic comments must be submitted on or before [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL*

REGISTSER]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery date service acceptance receipt is on or before that date:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2018-N-0791 for "Exposure-Response Analysis in Drug Development and Regulatory Decision Making; Request for Comments." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015,

or access the information at: <https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Kevin Krudys, Office of Clinical Pharmacology, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51; Rm. 3110, Silver Spring, MD 20993-0002, 301-796-3859, OCP_EPPM_STAFF@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

On May 6, 2003, FDA issued a GFI entitled "Exposure-Response Relationships--Study Design, Data Analysis, and Regulatory Applications" (available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072109.pdf>) (68 FR 24004). This guidance provides recommendations for sponsors of investigational new drugs (INDs) and applicants submitting new drug applications (NDAs) or biologics license applications (BLAs) on the use of exposure-response analyses in the development of drugs, including therapeutic biologics. Since then, FDA and drug developers have gained a wealth of experience performing exposure-response analyses and leveraging the results to influence drug development and inform regulatory review. Additionally, obstacles that limit the routine application and acceptance of exposure-response analyses to address key drug

development and regulatory decisions have since been identified. Given that PDUFA VI goals highlight advancing MIDD, FDA wants to capture the public's experience to inform future efforts on providing additional clarity, new insights, and updated recommendations for employing exposure-response analyses in drug development. To achieve these ends, FDA is opening the docket "Exposure-Response Analysis in Drug Development and Regulatory Decision Making: Request for Comments" to give interested parties an opportunity to identify areas of scientific policy that may need further clarity or elaboration, as well as any obstacles preventing use of exposure-response analyses in drug development and regulatory review.

II. Additional Issues for Consideration: Request for Information and Comments

Interested persons are invited to provide detailed information and comments on the use of exposure-response analysis in drug development and regulatory review. FDA is particularly interested in responses to the following questions:

1. In general, are there any aspects of the 2003 GFI entitled "Exposure-Response Relationships--Study Design, Data Analysis, and Regulatory Applications" that merit further elaboration? Additionally, are there any new topic areas that should be addressed?
2. What are best practices for conducting exposure-response analysis that can be generally applied across development programs and regulatory submissions? Input on best practices can include any of the following topic areas:
 - Planning and design (e.g., data considerations, assumption setting);
 - Analytical approaches (e.g., exposure and response metrics, choice and inclusion of predictors, methods for addressing confounding factors);

- Model evaluation and qualification (e.g., goodness-of-fit, assessment of model risk, impact on regulatory decisions); and
 - Communication of results and impact on subsequent drug development or regulatory decisions.
3. What attributes of an exposure-response analysis are critical to effectively inform a drug development or regulatory decision? Additionally, what are the main obstacles preventing widespread acceptance of exposure-response analyses?
 4. During which stages of drug development would it be most productive to interact with the FDA regarding exposure-response analysis planning? What type of feedback would be useful to inform exposure-response analyses and to reduce uncertainty in regulatory acceptance?

FDA will consider all information and comments submitted.

III. Electronic Access

Persons with access to the internet may obtain the 2003 GFI entitled "Exposure-Response Relationships--Study Design, Data Analysis, and Regulatory Applications" at either <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072109.pdf> or <https://www.fda.gov/Drugs/GuidancecomplianceRegulatoryInformation/Guidances/default.htm>.

Dated: April 2, 2018.

Leslie Kux,

Associate Commissioner for Policy

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